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BEFORE THE BOARD OF PATENT APPEALS
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Application Number: 09/667,859
Filing Date: September 20, 2000
Appellent(s): KUBIN ET AL.

MIDDLEN & CARROLL, LLP
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed NOVEMBER 24, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

Issue 1 – Whether Claims 73, 74, 80, 84-89 are enabled under 35 USC § 112, first paragraph of scope of enablement.

Issue 2 – Whether Claims 73, 74, 80, 84-89 are supported by an adequate written description under 35 USC § 112, first paragraph.

Issue 3 – Whether Claims 73-78 and 80-89 are patentable under 35 USC § 103(a) over Valiante et al. (U.S. Pat. No. 5,688,690A), Sambrook et al. (Molecular Cloning A laboratory Manual, 2nd edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43-2.84) and Porunelloor et al. (J. Immunol. 1993, Vol. 151, pp. 5328-5337).

Issue 4 – The rejection of claims 73-84 under 35 U.S.C. 112 second paragraph is hereby withdrawn.

(7) Grouping of Claims

Office agrees with the grouping that the rejection of claims 73, 84 and 85 stands or falls together because appellant's brief includes a statement that this grouping of claims stands or falls together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

US Patent No. 5,688,690A	Valiante et al.	November 18, 1997
US Patent No. 6,159,711A.	Proudfoot et al.	December 12, 2000

Robin et al. The Cytokine FactsBook, Academic Press 1994, pp 189.

Struyf et al. "Natural truncation of RANTES abolishes signaling through the CC chemokine receptor CCR1 and CCR3 impairs its chemotactic potency and generates a CC chemokine inhibitor" Eur. J. Immunol. 1998, Vol. 28, pp. 1261-1271.

Porunelloor et al. " Cloning and Characterization of the 2B4 Gene Encoding a Molecule Associated with Non-MHC-Restricted Killing Mediated by Activation Natural Killer Cells and T Cells" J. Immunol. 1993, Vol. 151, pp. 5328-5337.

Sambrook et al. Molecular Cloning A Laboratory Manual, 2nd edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43-2.84.

(10/1) Ground of Rejection of Issue 1

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 73, 74, 80, 84-89 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for an isolated nucleic acid molecule of SEQ IN NO: 1 that encodes the amino acid sequence of SEQ ID NO: 2 (NAIL), and the functional fusion proteins of amino acid residues 1-221 of NAIL fused with different tags (SEQ ID Nos: 6-8), does not reasonably provide enablement for any or all polynucleotides having at least 80% identity to SEQ ID NO: 1 or any or all polypeptides having at least 80% identity to the amino acids 22-221 of SEQ ID NO: 2, wherein the coding polypeptides thereof still functionally bind to CD48. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

2. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

3. 1) &2) State of art and unpredictability of the field.

4. The method for isolating a molecular clone is well known in the art by using a cDNA probe or by using an antibody. However, it is also known in the art that the isolated DNA molecules even under the same condition from the same cDNA library can be structurally and functionally different. The art also teaches that although some proteins exhibit a strong homology each other, they can be functionally different biological molecules.

5. For example, the amino acid sequences of human chemokines MIP-2α, MIP-2β and human GRO/MGSA as disclosed by Robin et al. (The cytokine Factors Book, Academic Press 1994, pp. 189) exhibit high homology between the human proteins (87%). However, they are totally functional different molecules. For instance, MIP-2 chemokine is a growth factor for myelopietic cells, whereas, GRO/MGSA is a growth factor for fibroblasts and melanoma cells. (See lines 1-19 on page 188).

6. This unpredictability is also demonstrated that even one amino acid mutation in a polypeptide can completely change its biological function and become another patentable distinct subject as evidenced by Struffy et al. (Eur. J. Immunol. 1998, Vol. 28, pp. 1262-1271) and Proudfoot et al. (US Patent 6,159,711A). Struffy et al. demonstrate that human chemokine RANTES lacking two N-terminal residue (3-68) looses its chemotactic activity (Fig. 2 on page 1261). Proudfoot et al. et al. disclose that the N-terminal modification RANTES with methionine (Meth-RANTES) or Leucine (Leu-RANTES) change the mutated RANTES as an antagonist of native RANTES, which exhibits a higher affinity for HIV-1 co-receptor CCR5, competes with native RANTES and blocks HIV-1 infection (see line 34 on col. 6 through line 67 on col. 8).

7. 3) Number of working examples and amount of guidance:

8. The specification only teaches an isolated the DNA sequence (SEQ ID NO:1 for cDNA and SEQ ID NO: 3 for the complete DNA sequence) that encodes a 38 Kd protein of NAIL (SEQ ID NO: 2) by using the C1.7 monoclonal antibody. The specification also discloses the soluble fusion proteins that contain the extracellular domain of amino acid residues 1-221 fused with different tags (NAIL-Fc polypeptide of SEQ ID NO: 6, see lines 14-18 on page 29; poly-histidine tags, NAIL-Flag-poly polypeptide of SEQ ID NO: 7, see lines 29-31 on page 25 and leucine zipper and poly-histadine tag, Nail-LZ-polyHis polypeptide of SEQ ID NO: 8). This extracellular domain of NAIL fusion proteins are only variants of the NAIL protein disclosed in the specification that are able to bind the CD48.

9. The specification does not teach any other nucleic acid molecule having at 80% identity to SEQ ID NO: 1 or any other polypeptide having at least 80% identical to 22- 221 amino acids of SEQ ID NO: 2 that encodes a functional polypeptide being able to bind CD48 like the full length of NAIL or the extracellular domain of NAIL.

10. The specification is deficient for teaching which 20% or 19% of amino acid residues should be changed in order to maintain the biological function for binding to CD48.

11. 5) Scope of the claims:

12. The claims broadly read on any or all nucleotide sequence having more than 80% identical to SEQ ID NO: 1 or any or all polypeptides having at least 80% identical to 22- 221 amino acids of SEQ ID NO: 2, which encodes a functional polypeptide being able to bind CD48 like the full length of NAIL or the extracellular domain of NAIL.

13. 6) Nature of the invention:

14. The claimed invention is directed to a structurally and functionally unique molecule and variants thereof having a particular biological function of biding to CD48 receptor and activating non-MHC restricted NK cell killing.

15. 7) Level of the skill in the art:

16. The technique requirement of claimed invention is related to the molecular cloning and isolating a functional biological molecule. Without adequate teaching and guidance, a significant hurdles remain to be overcome in order for a skilled artisan to practice successful the full scope of claimed invention.

17. Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the full scope of the claimed invention.

(11/1) Response to Argument of Issue 1

18. Appellants argue that the Office has failed to establish a prima facie case of non-enablement because (1) the Office's arguments bear no relationship to the disclosure of the specification at issue; (2) the Office arguments lack of an application of the Wands factors to support the conclusion that the claims are enabled; (3) the Office's arguments fail to consider the limitation of claims 75-78 and 81-83; and (4) the Office has ultimately failed to present an argument that is well grounded in scientific reasoning or evidence.

19. Regarding the above argument (3) directed to claims 75-78 and 81-83, the rejection on these claims is removed.

20. In response to Appellant argument (1) that Office made an inappropriate analogy to data for a complete protein and did not explain why this unrelated data is more persuasive on the issue of enablement than the actual teaching of the specification, the examiner's answer is that because NAIL polypeptide is protein, it inherently has all characteristics of a protein, such as a random mutation of amino acid(s) can be unpredictable for maintaining its original biological function as evidenced by Struffy et al. (Eur. J. Immunol. 1998, Vol. 28, pp. 1262-1271) and Proudfoot et al. (US Patent 6,159,711A) discussed supra.

21. Regarding the argument (2) that Office Action lacks of an application using Wands factors to support the conclusion that all claims are enabled, the Appellant is reminded that the Office Action, paper No. 7 mailed on February 27, 2002 had analyzed each of the Wands factors in detail. In response to the Office Action of paper No. 7, Applicants canceled all rejected claims 48-50, 54-57 and 59 and added new claims 73-89 on page No. 8, filed in on July 02, 2002. However, the broad scope of claims 73, 74, 80, 84-89 are still read on the rejected claims 48 and 59. Therefore, Office further explained the Wands factor in paper No. 9, mailed on September 20, 2002.

22. For example, in the Office Action of paper No: 7, the examiner wrote:

23. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

24. 1) &2) State of art and unpredictability of the field.

25. The method for isolating and identifying an DNA molecule is well known in the art by using a known DNA probe screening a DNA library at different hybridization condition or by using an antibody to screening a protein expressed by a cDNA library transfected cells followed by isolating the co-responding cDNA. However, it is also a common knowledge for art of molecular cloning that the isolated DNA molecules even with same probe under the same hybridization condition from the same cDNA library can turn out to be structurally and functionally different molecules. Furthermore, although some molecules exhibit a strong homology between each of the other, they still can be functionally different molecules.

26. For example, the amino acid sequence of human chemokines, such as MIP-2α, MIP-2β and human GRO/MGSA as disclosed by Robin et al. (The Cytokine FactsBook, Academic Press 1994, pp. 189) exhibit high homology among each other (87%). However, they are identified as totally functional different molecules. For instance, MIP-2 proteins are made by cytokine or LPS- activated monocytes, whereas the GRO/MGSA is made by activated monocytes, fibroblasts, epithelia and endothelia cells. MIP-2 chemokine is a growth factor for myelopietic cells. GRO/MGSA is a growth factor for fibroblasts and melanoma cells. (See lines 1-19 on page 188). Therefore, using homology, such as 80% to claim all different DNA molecules isolated by hybridization as the same functionally identical molecule is very unpredictable.

27. This unpredictability is also demonstrated that even one amino acid mutation in a polypeptide can render the mutated protein or polypeptide to be a functionally different molecule as evidenced by Struffy et al. (Eur. J. Immunol. 1998, Vol. 28, pp. 1262-1271), Proudfoot et al. (US Patent 6,159,711A). Struffy et al demonstrate that a nature form of human chemokine RANTES lacking two N-terminal residue (3-68) lost the chemotactic activity in monocytes and

eosinophile in comparison with the full length non-truncated RANTES (Fig. 2 on page 1261). Proudfoot et al. et al. teach that the N-terminal modification RANTES with methionine (Meth-RANTES) or Leucin (Leu-RANTES) change the mutated RANTES as an antagonist to the native RANTES, which exhibits a higher affinity for HIV-1 co-receptor CCR5 than native RANTES for blocking HIV-1 infection (See entire document).

28. 3) Number of working examples and amount of guidance:

29. The specification of current application only presents method for isolating the nuclei acid sequence (SEQ ID NO: 3) and coding sequence (cDNA, SEQ ID NO: 1) that encode a NK cell surface marker protein NAIL with molecule weight 38Kd NAIL of SEQ ID NO: 2 by using the commercial monoclonal C1.7 antibody identified Valiante in U.S. Pat. No. 5,688,690A. The specification only present the soluble fusion proteins of NAIL made by 1- 221 amino acids (extracellular domain) of NAIL fused with different kinds of tags (SEQ ID NOs: 6 and 8), which binds to the CD48 molecule (See lines 6-10 on page 71).

30. There is no working examples presented in the specification to illustrate that any or all nucleic acid molecules having at least 80% homology to the SEQ ID NO: 2 that is able to exhibit the same function as the full length of NAIL and the extracellular domain fusion polypeptide of NAIL.

31. 5) Scope of the claims:

32. The claims are very broad with the claims reciting any or all nucleotide sequence having more than 80% homology that encodes a polypeptide, which is able to bind CD48 molecule.

33. 6) Nature of the invention:

34. The instance application is directed to a structurally and functionally molecule and its functional variants. To enable this, the precise molecular structure being able to exhibit the same identical function should be disclosed.

35. 7) Level of the skill in the art:

36. Without adequate teaching, a significant hurdles remain to be overcome for practice the full scope of claimed invention.

37. In the Office Action, page No. 9 in response to the Applicant's argument, paper No. 8, filed in on July 02, 2002, the examiner further explained that while specification has described the general method of calculating the homology or identity of a possible variants of NAIL, it

does explicitly teach how to make each of the claimed products, for example, which 20% or 19% of amino acid can be varied and how to vary them etc.

38. Therefore, the Office did apply the Wands factors and use the scientific reasoning to concluded that an undue experimentation would be required in order for a skilled artisan to practice successful the full scope of the claimed invention.

39. Therefore, it is believed that the rejection should be maintained.

(10/2) Grounds of Rejection of Issue 2

The following ground(s) of rejection are applicable to the appealed claims:

40. Claims 73, 74, 80 and 84-89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of any or all polypeptides having at least 80% identity to the amino acid residue of 1-221 of SEQ ID NO:2 or any or all polynucleotide having at least 80% identity to the SEQ ID NO: 1, wherein the polypeptide or encoded polypeptide is able to bind the CD48.

41. The case law of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

42. In the instant disclosure, the specification only disclosed the nucleic acid sequences of SEQ ID NO: 1 and 3, in which SEQ ID NO: 1 encodes 38 Kd NK cell activation inducing ligand (NAIL) of SEQ ID NO: 2. The specification also teaches the functional soluble extrcellular domain of amino acid residues (1-221) of SEQ ID NO: 2. However, no other sequences, which having at lease 80% identity to amino acid 2-221 of SEQ ID NO: 2 or fragment thereof exhibiting the same function like NAIL is disclosed. While some homologue to SEQ ID NO: 1 or 2 can be isolated from other mammal origins; however, specification must reasonably convey to those skilled in the art that the applicant was in possession of the claimed invention as of the date of invention.

(11/2) Response to Argument of Issue 2

43. Appellant traverses the rejection and submits that the examiner has incorrectly applied the facts of Eli Lilly Co. since Appellant clones the human cDNA that encodes NAIL and identifies that NAIL is binding partner of CD48. Moreover, Applicants described a wide variety of variants of these molecules mutations, conserved changes, deletions, fusions to sequences encoded usually domains such as Fc's etc.) at page 17-33. Thus, it is clear that the inventor is contemplated and was in possession of the claimed invention.

44. Appellant's argument has been respectfully considered; however it is not found persuasive because the specification has been carefully reviewed, it only discloses an isolated full length NAIL DNA (SEQ ID NO: 3) or the cDNA of SEQ ID NO 1 that encodes the full length of amino acid sequence NAIL of SEQ ID NO: 2, wherein the NAIL polypeptide consists of a single peptide of amino acids 1-21 of SEQ ID NO: 2, and extracellular domain of amino acids 22-221 of SEQ ID NO: 2, a transmembrane domain of amino acids 222-245 of SEQ ID NO: 2, and cytoplasmic domain of amino acids 246-365 of SEQ ID NO: 2.

45. While the specification states that variants of NAIL can occur naturally or derived from the disclosed SEQ ID NO: 2, specification only teaches that the functional truncated NAIL polypeptide that binds to the CD48 is the extracellular domain fusion protein of NAIL (SEQ ID NO: 6-8). The receptor binding activity critically depends on the content of the extracellular domain of a ligand. However, the specification does not teach any other variants that exhibit more than 80% identity to the extracellular domain is able to bind to the CD48.

46. Appellant further argue that the specification of page 17-37 describes that NAIL can be mutated and the specification of example 14, page 53-55 discloses a single species of NAIL variant having at least 95% structural identity to SEQ ID NO: 3 that has actually been reduced to practice, and describe an assay for identifying the variants having the desired catalytic activity. Therefore, in order to determine whether one of skill in the art would determine the applicant was in the possession by the member of the genus only require of analysis of considers (1) whether the members of a genus vary substantially from each other; and the (2) whether the disclosed species is representative of the members of the genus.

47. Appellant's argument has been fully considered; however, it is not found persuasive because the specification has been carefully reviewed, it is found that the specification only

contains 11 examples and it does not have such a disclosure of a single species of protein having 95% structure identity to SEQ ID NO: 3 anywhere in the whole content. Furthermore, SEQ ID NO: 3 is not a protein sequence, it is the nucleic acid sequence of NAIL (See lines 32 on page 11 to lines 7 on page 13).

48. According to M.P.E.P. 2106, the satisfaction of the enablement requirement does not satisfy the written description requirement. See In re Barker, 559 F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977) (a specification may be sufficient to enable one skilled in the art to make and use the invention, but still fail to comply with the written description requirement). See also Inre DiLeone, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971). For the written description requirement, an applicant's specification must reasonably convey to those skilled in the art that the applicant was in possession of the claimed invention as of the date of invention. Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997); Hyatt v. Boone, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir. 1998).

49. In the instant case, while specification describes some methods used for determining the nucleic acid sequence identity and testing the CD48 receptor binding, Appellant is reminded that the enablement issue and the written description issue are separate in that specification of current application must reasonably convey to those skilled in the art that the appellant was in possession of the claimed invention as of the date of invention.

50. Regarding claims 84-89, because claims 84-89 depend on claim 73, the claim 73 is not in the possession of the claimed nucleic acid molecule; the dependent claims 84-89 directed to the vector or host cells comprising the nucleic acid molecule are also rejected.

51. For the reason described above, it is believed that the rejection should be sustained.

(10/3) Grounds of Rejection of Issue 3

The following ground(s) of rejection are applicable to the appealed claims:

52. Claims 73-78 and 80-89 are rejected under 35 USC § 103(a) as being unpatentable over Valiante et al. (U.S. Pat. No. 5,688,690A), Sambrook et al. (Molecular Cloning A laboratory Manual, 2nd edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43-2.84) and Porunelloor et al. (J. Immunol. 1993, Vol. 151, pp. 5328-5337).

53. Claimed invention is drawn to an isolated polynucleotide of SEQ ID NO: 1 that encodes a NK cell activation inducing ligand (NAIL) of SEQ ID NO: 2. The clone is isolated with

monoclonal antibody C1.7 (ATCC HB 117170) by screening a human NK cell lines transfected with a human cDNA library after the cell line is stimulated with cytokine IL-2, IL-12, IL-15, INF-γ or anti-CD16. The isolated DNA sequence encodes the 38 kD protein of SEQ ID NO: 2, which has molecular weight of 38 Kd and it can be recognized by the monoclonal antibody C1.7. The extracellular domain of NAIL (1-221 amino acid residues) and its full-length molecule are able to bind CD48 molecule.

54. Valiante et al. disclose a novel monoclonal antibody (Amb) C1.7 (ATCC HB 117170) that is able to recognize an antigen or cellular receptor, a 38 kD protein p38, which is expressed in a NK cell and other CD8+ T cell upon activation by cytokines, such as IL-2. Valiante et al. also disclose that the functions of p38 protein is to mediate a non-MHC-restricted cytotoxicity; stimulate the lymphocyte proliferation, lymphokine production, signal transduction of NK cells etc. (Please see examples 4-10). Valiante et al. also teach several potential utilities for the protein p38, such as for identifying other ligands, employing as therapeutically agent to block ligands biding to CD8 cell or inhibit the CD8 T cell activation and killing of target cells in the situation of a transplantation rejection or autoimmune destruction. The p38 also can be use for stimulating the immune response etc. (see the utilities of p38 disclosed in lines 8 on col. 8 through line 67 on col. 9).

55. Valiante et al. do not disclose the sequence of the p38 protein recognized by Amb C1.7. However, they stated that the DNA and protein sequence of p38 can be obtained by conventional methodologies known to one of skill in the art in view of the detail methods taught by Sambrook et al. (Molecular cloning A Laboratory Manual, 2nd edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43-2.84). Valiante et al. further explicitly teach the working examples (lines 48 on col. 7 through line 7 on col. 8 and examples 12 on col. 18 through 19) of isolating the cDNA clone by using Amb C1.7, screening the protein expression in the cell transfected with the cDNA library and cloning a corresponding cDNA into a plasmid for sequencing analysis.

56. Porunelloor et al. disclose an isolated mouse 2B4 molecule by using a molecule cloning method from mouse cDNA library. In addition, they teach that this molecule is related to the non-MHC restricted NK cell killing and is a highly conserved protein during the evolution. The human also has the homologue of the 2B4 molecule (See abstract, lines 23-27 on 1st col. of page 5335 and Fig. 6 on page 5336).

57. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited reference of Valiante et al. and Porunellor et al. to further adapt the methods taught by Valiante et al. or Sambrook et al. to isolate the nucleic acid sequence corresponding to the conserved p38 protein by either using the monoclonal antibody or DNA probe. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

(11/3) Response to Argument of Issue 3

58. Appellant argues that the Office Action is in error because the Office failed to establish a prima facie case of obviousness with respect to any of the pending claims for the following reasons: (1) The cited references do not teach each element of the claims and (2) the Office has not shown no evidenced of a motivation to combine the references.

59. Regarding to the argument (1), Appellant asserted that references cited by Office failed to teach a single nucleic acid molecule encoding a polypeptide at least 80 or 90% identical to 22-221 of SEQ ID NO: 2 as required by claims 73, 74, and 84-89 and Office provided no evidence establishing that none of the three references discloses a nucleic acid molecule even remotely related to the claimed sequences. Appellant further submitted that the situation of the instant case has a similar situation off In re Deule (34 USQ2d, 1212) because "the existence of a general method of isolating cDNA or DNA molecule is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious..." Appellant also asserted that it is not proper for the examiner to use p38 protein identified in the "690" patent together with the methods described in the references to reject claims drawn to specific sequences.

60. Appellant's argument has been respectfully considered; however, it is not found persuasive because claimed invention is drawn to a polynucleotide of SEQ ID NO: 1 isolated from cDNA library of human NK cells and human NK cells stimulated with IL-2, IL-12, IL-15, INF-γ or anti-CD16 by using the commercial monoclonal antibody C1.7 (ATCC HB 117170) disclosed by Valiante et al. The cDNA of SEQ ID NO: 1 encodes a 38 Kd protein NAIL of SEQ ID NO: 2, which is highly expressed in human NK cells and monocytic cell line U937 followed by CD8+ cells. NAIL binds to CD48 and the interaction of NAIL with CD48 enhances the activation of NK cells.

61. Valiante et al. disclose a novel monoclonal antibody (Amb) C1.7 (ATCC HB 117170) that is used for identify a protein with molecular weight of 38 Kd (p38). They teach that the monoclonal antibody C1.7 is able to recognize an antigen or cellular receptor of a 38 kD protein, which is a cell surface receptor or marker of NK cell upon activation by cytokines, such as IL-2. Valiante et al. also disclose the function of p38 is to mediate the non-MHC-restricted NK cell cytotoxicity; stimulates the lymphocyte proliferation, lymphokine production, signal transduction of NK cells and BLT-Esterase release from NK cells (Please see examples 4-10).

62. Therefore, there is no reason to suspect the NAIL and P38 are not the same proteins since they are recognized by the same monoclonal antibody in the same type of cells under the same biological condition. Moreover, NAIL and p38 have same molecular weight and exhibit the same biological function. A patent cannot issue to a genus of degenerate nucleic acid molecule where the protein polypeptide encoded thereby was known prior to the invention was filed. Because if a protein was known in the art, the structure is an inherent characteristic of the protein. It does not add any patentable weight for an invention for just sequencing a know protein in the art.

63. Regarding to Appellant's argument (2) that the Office has not shown an evidenced of a motivation to combine the references, Appellants alleged that Office use a hindsight-bases approach and provide no rationales as to why a person of ordinary skill in the art would be motivated to combine Valiante et al. Porunelloor et al. and Sambrook et al. Especially, there is no evidence indicating any relation between the references of Valiante et al. and Porunelloor et al.

64. In response to this argument, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

65. In the instant case, Porunelloor et al. teach that they have isolated a signal transducing molecule 2B4 from mouse cDNA library by using the hybridization approach. They found that the 2B4 is expressed on all NK and T cells that mediate non-MHC-restricted killing. By using Southern blot analysis with the isolated mouse 2B4 as a probe, Porunelloor et al. also found that

the 2B4 gene is somewhat conserved during evolution, and they further demonstrated that human has a homologue gene to the mouse 2B4 gene (See lines 18-27 on 1st col. of page 5335, Fig. 6 on page 5334 and abstract).

66. The patent by Valiante et al. provides a novel 38 kD signal transduction surface molecule (p38) expressed by virtually all human NK cells, which is capable of binding to, and activating the NK cells (See abstract, lines 5-25 on col. 4, line 6 on col. 5 to line23 ob coll. 9). Valiante et al. also disclose the function of p38 is to mediate the non-MHC-restricted NK cell cytotoxicity; stimulates the lymphocyte proliferation, lymphokine production, signal transduction of NK cells and BLT-Esterase release from NK cells (Please see examples 4-10). Valiante et al. also teach several potential utilities of the novel protein p38, such as to identify other ligands or block ligands to CD8 cell and inhibit the CD8 T cell killing of target cells in the situation of a transplantation rejection or autoimmune destruction (see the utilities of p38 disclosed in lines 8 on col. 8 through line 67 on col. 9).

67. Therefore, both reference of Valiante et al. and Porunelloor are focused on a conserved cell surface signaling molecule that mediates the non-MHC-restricted NK cell killing activity. Valiante et al. teach the human version and Porunelloor teach the mouse version. The person with the ordinary skill in the art would have been motivated by the cited references to search this conserved cell surface signaling molecule because the non-MHC restricted NK cell mediated killing is very important in the field as taught by Valiante et al. and Porunelloor et al.

68. While Valiante et al. do not disclose the sequence of the protein recognized by mAb C1.7, they teach in the Patent that the DNA and protein sequence of p38 can be obtained by using the conventional methodologies known to one of skill in the art in view of the detail methods taught by Sambrook et al. (Molecular cloning A Laboratory Manual, 2nd edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43-2.84). Valiante et al. also explicitly teach the working examples (lines 48 on col. 7 through line 7 on col. 8 and examples 12 on col. 18 through 19) for isolating the cDNA clone encoding the protein p38 by using Amb C1.7 and cloning the corresponding cDNA into a plasmid for sequence analysis etc.

69. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited reference of Valiante et al. and Porunelloor et al. and further combine the methods taught by Sambrook et al. to isolate the nucleic acid

encoding the protein by using either the monoclonal antibody or cDNA cloning method. Because both of references of Valiante et al. and Porunelloor et al. disclose the conserved protein that is associated with non-MHC restricted NK cell activation. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

70. For the reason above, it is believed that the rejection should be maintained.

Respectfully submitted,

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